Development of homogeneous catalysts for the selective conversion of levulinic acid to caprolactam

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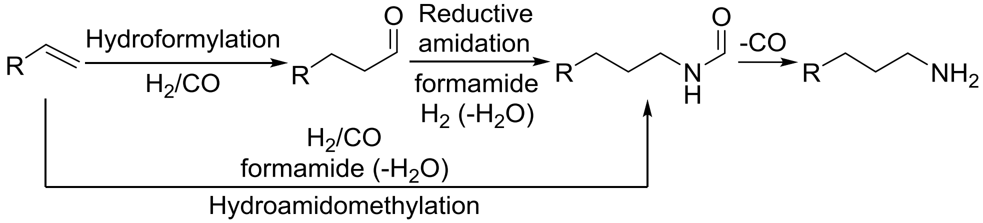
Towards Synthesis of Primary Amines: Investigating Rhodium-Catalyzed Homogeneous Reductive Amidation and Hydroamidomethylation with Formamide



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Raoufmoghaddam S.; Kortlever R.; Drent E.; Bouwman E.; manuscript in preparation

Abstract

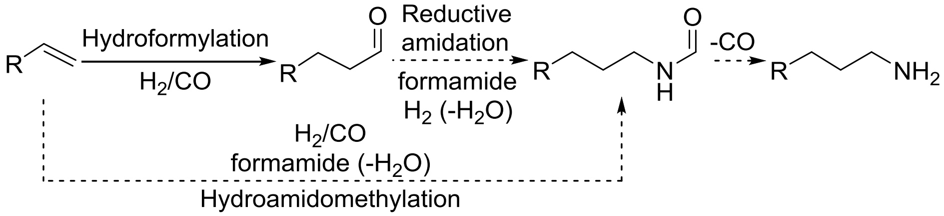
The catalytic reductive amidation of an aldehyde with formamide using Rh/xantphos/HOTs catalyst systems is reported, as part of an atom-efficient synthesis of primary amines from alkenes. Our studies on the reductive amidation of hexanal with formamide revealed a catalytic performance characteristically different from the reductive amidation of hexanal carried out with higher alkylamides. To achieve similar catalytic performance of the Rh/xantphos catalyst system with formamide, the strong acid HOTs component needed to be significantly increased. Under these modified conditions, a good overall selectivity to the desired N-hexylformamide (~80%) was observed while the catalytic reduction *specificity* for production of N-hexylformamide over hexanol was spectacularly increased with the higher HOTs concentrations up to a ratio N-hexylformamide/hexanol of ~60-80. More importantly, the reductive amidation reaction of aldehydes with formamide as the substrate can be applied to a wide range of aldehydes.

Hydroamidomethylation of an alkene (1-pentene) with formamide, involving both hydroformylation and reductive amidation of the produced aldehydes, has also been investigated. Experiments with a Rh/xantphos/HOTs catalyst system promoted by 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HOR^F), however, thus far revealed much poorer yields (~20%) to N-hexylformamide relative to those of N-hexylamides obtainable with higher alkylamides (up to 80%) under the same reaction conditions. Clearly, HOR^F is a less efficient hydrogenation promoter in hydroamidomethylation with formamide relative to acetamide as the amide substrate. It is suggested that the cause for the poorer performance in hydroamidomethylation lies in the lower nucleophilicity at N of formamide relative to higher alkyl amides. The higher acidity required for efficient reductive amidation with formamide of the intermediate aldehydes now causes HOR^F to less efficiently promote hydroamidomethylation, most likely due to its excessive (acid-catalysed) acetalisation with the aldehydes. Using N-hexylformamide as a source of n-hexylamine by decarbonylation was demonstrated by using some transition metal complexes or strong base. However, until now only stoichiometric conversions with either transition metal complexes or strong base could be obtained under the conditions applied.

4.1. Introduction

The formation of carbon-nitrogen bonds is of particular academic and industrial interest because it offers synthetic potential to a wide range of useful products in synthetic chemistry, biology, pharmaceuticals and material science.[1] Nitrogen-containing compounds, such as amines and more specifically primary amines are applied for the production of valuable bulk chemicals, dyes, pharmaceuticals and biologically active compounds.[2] Among the different catalytic methods of carbon-nitrogen bond formation, the most studied methods are hydroamination of alkenes and alkynes with amines,[2-5] hydroaminomethylation of alkenes[6-10] and the reductive amination of carbonyl compounds.[11-17] In principle, these reactions can be performed without or with very limited waste formation, fulfilling one of the requirements of 'green' chemistry. Despite recent developments in the synthesis of substituted amines,[2, 18, 19] the catalytic synthesis of primary amines is still a challenge in terms of energy usage as well as atom-efficiency.[20, 21] The currently used industrial process of making primary amines is based upon the catalytic amination of an alcohol or aldehyde with ammonia. This process holds some serious drawbacks such as employing high ammonia pressure and high temperature, thus leading to low efficiency.[22] Reductive amination of aldehydes and hydroaminomethylation of alkenes with ammonia generally suffers from over-alkylation.[14, 21] The initially produced primary amine is generally more nucleophilic and reactive than ammonia, thus resulting in the formation of substantial amounts of the secondary and tertiary amines. One approach to avoid over-alkylation has been to apply a large excess of ammonia. This method thus necessitates the application of high pressures at the required elevated reaction temperatures; excessive heavy-ends formation due to base-catalyzed aldol condensation reactions as well as energy-demanding product separations will thus generally be a consequence leading to high manufacturing costs.[14, 20, 21] The development of a new synthesis method for primary amines, avoiding over-alkylation, would be highly desirable.

Led by our recent discoveries of the catalytic reductive amidation of an aldehyde with acetamide (Chapter 2) and hydroamidomethylation of an alkene with acetamide (Chapter 3), we now propose a new synthesis route to obtain a primary amine from an alkene (Scheme 4.1). Aldehydes as intermediate products (after initial hydroformylation of alkene in the hydroamidomethylation reaction) can undergo a catalytic reductive amidation reaction with formamide to give N-alkylformamide, which can be subsequently converted into the corresponding primary amines via a decarbonylation process. Reductive amidation (in contrast with reductive amination) of an aldehyde generally avoids over-alkylation due to the low nucleophilicity and steric encumbrance at the amide N of the initially formed mono-alkylated product (Chapter 2 and 3).[23, 24]



Scheme 4.1. Proposed catalytic formation of N-alkylformamide and subsequent decarbonylation to primary amine

In this Chapter, we report our studies towards the catalytic reductive amidation reaction of hexanal with formamide and the hydroamidomethylation of pentene with formamide to form N-hexylformamide as well as the subsequent decarbonylation of N-hexylformamide leading to the formation of n-hexylamine.

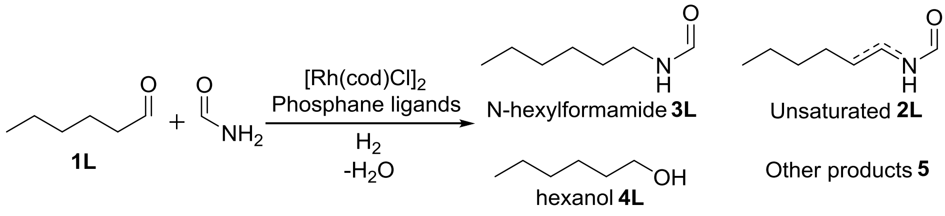
4.2. Results and Discussion

4.2.1. Reductive amidation of hexanal with formamide

The products found in a typical reductive amidation experiment with hexanal and formamide are shown in Scheme 4.2. Apart from the desired N-hexylformamide **3L**, the two isomeric unsaturated compounds N-(1-hexylidene)formamide or N-1-hexenylformamide **2L** as well as hexanol **4L** were observed.[25] Furthermore, formation of various products with higher mass, comprising condensation products **5** were also observed (Figure 4.1).

The reductive amidation experiments were performed starting with 5 mmol of hexanal and a small excess of formamide (6 mmol); a quantitative product distribution was determined from GC analysis. The hexanal conversions shown in the Tables were calculated from the amount of hexanal found in the reaction mixtures after the reaction.

Amounts of N-hexylformamide **3L**, unsaturated intermediates **2L**, and hexanol **3L** were determined using calibration lines.



Scheme 4.2. An overview of the reductive amidation of hexanal with formamide; formation of intermediates and products

The remainder consists of the higher mass products **5**, which were not individually quantified from GC, but rather calculated as a lumped-together number from the uneven mass-balance of hexanal-derived GLC-measurable products. The specificity of the catalysts for reductive amidation versus hydrogenation of hexanal is given as the ratio **3L**/**4L**. Full analytical data of all reaction mixtures are given in Appendix III.

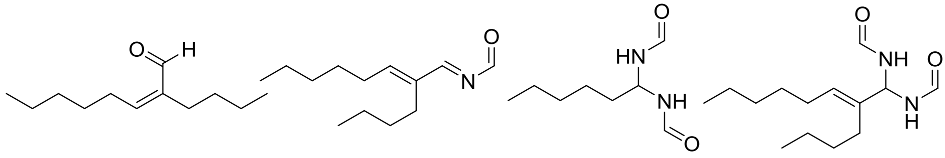


Figure 4.1. Products of higher molecular mass (**5**) observed in the reductive amidation reaction

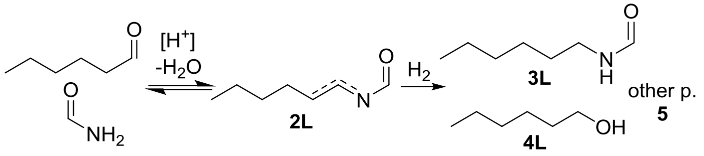
Led by our recent work on the reductive amidation of hexanal with acetamide and higher alkylamides (Chapter 2),[23] we started our exploratory batch test studies using similar conditions (Table 4.1, Entry 1). Under this condition (80 °C, 80 bar H_2, 0.05 mmol, HOTs/Rh~5), the reaction turned out to yield 66% selectivity to the desired **3L**, but with only ~35% conversion of hexanal **1L** and a relatively low **3L**/**4L** ratio (10). The relatively low yield of **3L** of only ~20% observed in reductive amidation with formamide can be seen as a negative extrapolation of the general trend described in Chapter 2 that *increased* yields of the N-alkylamide **3** are obtained with the *more* electron-donating alkyl groups at the amide (up to 90% with higher alkyl amides).[23]

In attempts to remedy the relatively low efficiency of the reductive amidation with formamide, we found that increasing the amount of HOTs co-catalyst to 0.8 mmol (thus increasing the HOTs/Rh ratio from 5 to 80) positively affects both the **3L**/**4L** product ratio (from 10 to 75) as well as the conversion of hexanal **1L** (from 33% to 85%); the overall yield for the desired **3L** was thus significantly increased from a modest 20% up to ~65% (Entries 1-6). Whereas the catalyst's reduction *specificity* for producing **3L** over **4L** gradually increased with acid concentration, the overall *yield* of **3L** leveled off at the higher acid concentration range, predominantly due to increased formation of condensation products **5**, in particular the product hexyl-di-amide. The necessity of using a higher acid co-catalyst concentration for obtaining an acceptable conversion to **3L** when formamide is used as the substrate, can likely be interpreted as being linked to the reduced nucleophilicity at N of formamide vs. a higher alkylamide. Nucleophilicity of the amide N in $HCONH_2$ vs $RCONH_2$ likely plays a role at two levels in the mechanism of reductive amidation of aldehydes.[23] First, a reduced nucleophilicity makes addition of the amide's N-H to the aldehyde carbonyl to form the intermediate unsaturated products **2L,** a higher barrier process. Secondly, the nucleophilicity may play a role in the fate of the -C=N-(CO-) imido-moiety at the Rh/xantphos hydrogenation catalyst. This leads to an intrinsically reduced rate of hydrogenation of the functionality, due to both a reduced binding strength to the cationic Rh/xantphos center and an increased barrier for migratory insertion of the -C=N-(CO)- moiety into the Rh-H bond.

As reported in Chapter 2,[23] we identified a dual functional role of the co-catalyst HOTs: First of all, the acid HOTs co-catalyst was shown to catalyze the amide-aldehyde addition reaction to produce intermediates **2.** The supposedly higher barrier for this process with formamide must be compensated by a higher concentration of the acid co-catalyst. Furthermore, the addition of excess of acid HOTs (up to ~80 fold) to the Rh/xantphos catalyst system will also generate a more cationic $[Rh^{III}(OTs)_n/xantphos]^+$ species in a more polar acidic environment, which together are held responsible for the efficient and selective hydrogenation of the imido intermediates **2** in the presence of aldehyde, thus being responsible for the high reduction specificity as indicated by the high **3L**/**4L** product ratio.

Application of different reaction temperatures revealed that lowering of the reaction temperature from 100 °C to 60 °C led to a further increase in selectivity for **3L**, from ~70% up to 85% (Entries 3, 9, 10). Upon further lowering of the reaction temperature to 40 °C the relative amount of unsaturated intermediates **2L** increased, thus indicating that the hydrogenation rate from **2L** to **3L** decreased (Entry 8). A temperature of 60 °C apparently is the optimal reaction temperature to obtain a high selectivity to **3** (85%) with a very high **3L**/**4L** product ratio (~60) at only slightly lower conversion of hexanal (66%). In fact, these optimized results are comparable with those obtained in the reductive amidation of hexanal with acetamide, applying the same conditions.

Table 4.1. Reductive amidation of hexanal with formamide catalyzed by $[Rh(cod)Cl]_2$ in combination with xantphos ligand [a]



	T	P (H_2)	HOTs	conversion	selectivity %[b]				**3L/4L**
	°C	bar	mmol	%	**2L**	**3L**	**4L**	**5**	ratio
1	80	80	0.05	33	15	66	7	12	10
2	80	80	0.1	57	9	76	4	11	19
3	80	80	0.2	70	5	81	2	12	41
4	80	80	0.4	79	8	76	1	14	60
5	80	80	0.6	81	8	76	1	14	78
6	80	80	0.8	85	7	74	1	18	75
7[c]	80	80	0.2	76	5	73	2	21	45
8	40	80	0.2	38	55	40	1	4	41
9	60	80	0.2	66	8	85	1	5	59
10	100	80	0.2	79	6	72	5	17	15
11	60	60	0.2	62	18	70	1	11	61
12	60	40	0.2	58	27	62	1	10	56
13	60	20	0.2	53	48	36	1	16	53
14[d]	60	80	0.2	72	25	61	1	13	47
15[e]	60	80	0.2	86	5	87	1	6	60

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol formamide (Rh:xantphos:hexanal: formamide=1:1.25:500:600); HOTs: 0.05-0.8 mmol;P_{H2}= 20-80 bar; T= 40-100 °C; t = 4 h; Solvent: 25 mL diglyme; [b] the selectivity was determined using decane as internal standard; [c] 7.5 mmol formamide; [d] 15 mLdiglyme; [e] 8 h; for more information see Appendix III, Table AIII.1

Applying a same low reaction temperature of 60 °C and a relatively high concentration of the co-catalyst HOTs (HOTs/Rh=20) led to a similarly high N-hexylacetamide/hexanol ratio and a selectivity to N-hexylacetamide of 90% at 83% conversion.

Lowering of the hydrogen gas pressure from 80 to 20 bar resulted in a significantly reduced overall hydrogenation activity of the catalytic system, thus resulting in a pronounced decrease in the selectivity to **3L** (from 85% to 36%) and increase in the formation of intermediates **2L** as well as other products **5** (Entries 3, 11, 12, 13). The use of more concentrated reaction media resulted in slightly higher conversion, but with the formation of higher amount of other products (entry 14). After 8 hours under optimized conditions (60 °C, 80 bar H_2) 86% conversion of hexanal with 87% selectivity to **3L** was achieved (Entry 15).

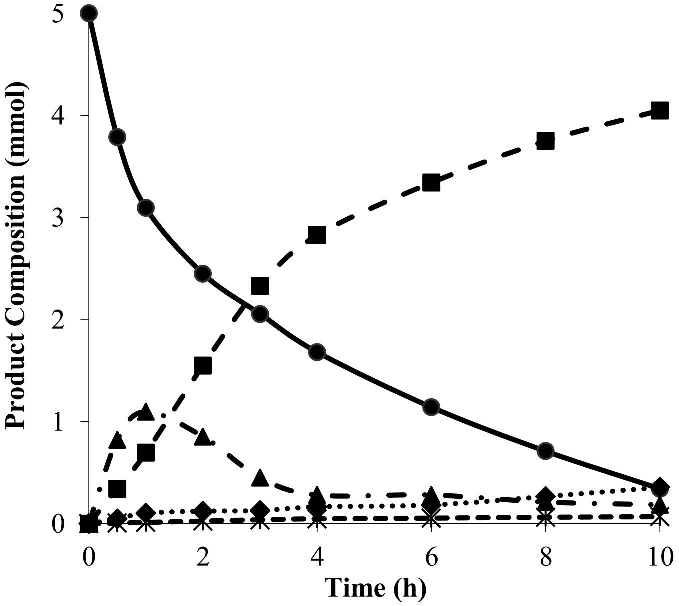
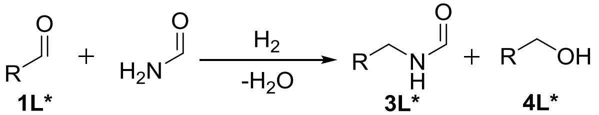


Figure 4.2. Product development in time in the reductive amidation of hexanal with formamide; Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.2 mmol HOTs, 5 mmol hexanal, 6 mmol formamide (Rh:xantphos:HOTs:hexanal:formamide=1:1.25:20:500:600); P_{H2}= 80 bar; T= 60 °C; Solvent: 25 mL diglyme; decane as internal standard. ●=hexanal (**1**), ■= N-hexylformamide (**3**), ▲=unsaturated intermediates (**2**), ♦= hexanol (**4**), ∗= other products (**5**)

The use of various other ligands in the catalytic system has been briefly explored (See Tables AIII2.1 and AIII2.2). As also established in Chapter 2 and 3,[23] the xantphos-type ligands appear to play a unique role in the Rh catalysed reductive amidation reaction.

The product development in time for the Rh/xantphos/HOTs catalytic system is depicted in Figure 4.2. After ten hours at 60 °C and a HOTs/Rh ratio of 20 nearly full conversion (~95%) is reached with 87% selectivity to **3L** and a product ratio of 60 for **3L**/**4L** (See Table AIII.3). It is shown that under the acidic conditions applied the amount of unsaturated intermediates **2L** builds up significantly in the first hour of the reaction (to about 20% of the initial hexanal intake). The build-up of **2L** suggests that under the strongly acidic, low temperature conditions applied with formamide, the reduction of the imido intermediate **2L** to give **3L** becomes overall rate determining.

Table 4.2. Scope of reductive amidation with formamide using various aldehydes[a]



	aldehyde 5 mmol	conversion %	selectivity % 2L*	3L*	4L*	5*	3L*/4L* ratio
1	butanal	86	8	82	1	9	61
2	hexanal	86	5	87	1	6	60
3	heptanal	85	6	81	1	11	58
4	octanal	83	6	81	2	12	54
5	nonanal	82	5	84	1	9	57
6	2-Me-pentanal	35	29	44	11	16	4
7	PhCHO	25	25	27	9	40	3
8	3-Ph-propanal	85	8	79	2	11	37

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.2 mmol HOTs, 5 mmol aldehyde, 6 mmol formamide (Rh:xantphos:HOTs:aldehyde:formamide= 1:1.25:20:500:600); P_{H2}= 80 bar; T= 60 °C; t= 8 h; Solvent: 25 mL diglyme; decane as internal standard

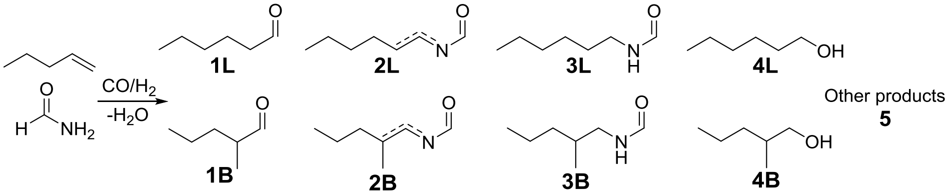
A number of different aldehyde substrates were applied in the reductive amidation reaction with formamide (Table 4.2). The use of aldehydes with a linear electron-donating alkyl group (butanal - nonanal) resulted in high selectivity (>80%) and conversion (>80%) with excellent ratios of **3L***/**4L*** (Entries 1-5). The use of bulkier aldehydes, such as branched 2-methylpentanal and benzaldehyde with an electronically different carbonyl moiety, were considerably less reactive in reductive amidation with formamide; not only the conversion of aldehyde was lower, but also the hydrogenation activity and substrate specificity (ratio **3L*/4L***) drastically decreased (Entries 6, 7). Furthermore, the use of 3-phenylpropanal with similar steric hindrance and electronics of the carbonyl group in linear paraffinic aldehydes, resulted again in high conversion (85%) accompanied by high selectivity to **3L*** (~80%) with only slightly lower **3L*/4L*** product ratio (Entry 8). Clearly, both the steric hindrance at the carbonyl and the electronic of the carbonyl group of the aldehyde substrates play an important role in the success of the reductive amidation of aldehydes with formamide (for detailed information see Table AIII.4), in fact similar to that with higher alkylamides under lower acidic conditions as shown in Chapter 2.[23]

4.2.2. Hydroamidomethylation of 1-pentene with formamide

As reported in Chapter 3 Rh/xantphos complexes catalyze the direct tandem hydroformylation-reductive amidation reaction (hydroamidomethylation) of alkenes, if acidic promoters, such as 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HOR^F) are applied in combination with diglyme and HOTs as a co-catalyst. Under these conditions, reductive amidation of the *in-situ* formed aldehydes could efficiently take place in the presence of syngas. In the reactions with 1-pentene and formamide as substrates (Table 4.3), however, this turned out to give much poorer selectivities to the desired **3L** (less than 20%) than obtainable with acetamide and higher alkylamides (>80%). Increasing the amount of HOR^F promoter did indeed show a promoting effect on the hydroamidomethylation reaction with formamide, but highest yields of **3L** were still slightly less than 20% based on 1-pentene. It was noted that significant formation of acetal (produced from the reaction of the in situ formed aldehyde with HOR^F) took place (up to ~25% yield). Clearly, the relatively high concentration of strong acid HOTs, necessary with formamide as substrate for more efficient reductive amidation, now also catalyzes extensive acetal formation of hexanal with HOR^F with the associated production of water ($RCOH + 2\ HOR^F \leftrightarrows RC(OR^F)_2 + H_2O$). As acetal formation is an equilibrium reaction, the very existence of the acetal itself is not considered a likely reason for limiting the yield of **3L**. It is however more likely that the associated H_2O production must be seen as the origin of low yield of **3L** as it opposes the in-situ formation of imido intermediates **2L**. It was shown in Chapter 3 that addition of even small amounts of water already has a significantly negative effect on the yield of hydroamidomethylation product **3L**, even with acetamide as a more nucleophilic amide substrate.[24]

Therefore, in order to suppress acetal formation, and more importantly H_2O formation, we decreased the amount of HOTs co-catalyst again from 0.2 mmol to 0.05 mmol in attempted hydroamidomethylation of 1-pentene with formamide. However, this resulted in even lower yields of the desired hydroamidomethylation product **3L** (cf. entries 6-8), thus re-confirming the need for a relatively high HOTs concentration with formamide in reductive amidation, also in tandem hydroformylation-reductive amidation under syngas conditions. It is clear that alternative hydroamidomethylation catalyst promoters should be examined to overcome the above sketched catalytic dilemma.

Table 4.3. Hydroamidomethylation of 1-pentene with formamide catalyzed by $[Rh(cod)Cl]_2$ in combination with xantphos ligand [a]



	diglyme/HOR^F 10 mL (v/v)	T °C	P (CO/H_2) bar	HOTs mmol	conv. %	selectivity %^{b}						1	3
						1	**2**	**3**	**4**	**acetal**	**5**	L%	L%
1	8/2	60	50(1/2)	0.2	58	72	9	5	0	5	9	98	>99
2	8/2	80	50(1/2)	0.2	73	68	8	6	0	10	8	98	>99
3	10/0	100	50(1/2)	0.2	83	44	14	4	1	0	37	97	>99
4	9/1	100	50(1/2)	0.2	84	43	10	7	1	13	27	97	>99
5	7/3	100	50(1/2)	0.2	84	41	6	11	1	26	14	97	>99
6	8/2	100	50(1/2)	0.2	87	40	8	20	0	20	12	95	>99
7	8/2	100	50(1/2)	0.1	87	54	8	15	0	13	10	95	>99
8	8/2	100	50(1/2)	0.05	86	64	7	12	0	8	9	96	>99

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol 1-pentene, 5 mmol formamide (Rh:xantphos:1-pentene: formamide=1:2:500:500); HOTs: 0.05-0.2 mmol;P(CO/H_2)= 50 (1/2) bar; T= 60-100 °C; t = 8 h; Solvent: 10 mL diglyme or diglyme/HOR^F; ^{b} the selectivity was determined using decane as internal standard; for more information see appendix III, Table AIII.5

4.2.3. N-alkylformamides to primary amines

We considered that the mono-N-alkylated formamide products, shown to be accessible by the reductive amidation of aldehydes and in a lesser extend by hydroamidomethylation of alkenes with formamide, in principle could serve as a convenient source of primary amines through a decarbonylation process. Decarbonylation is well-known for aldehydes,[26-29] methyl formate[30-32] and dimethylformamide (DMF).[33-36] Aldehyde decarbonylation was first discovered as a stoichiometric organometallic reaction[37-41] and was then developed into a catalytic process[27, 28] with the help of transition metal complexes, mainly of rhodium, iridium, ruthenium and palladium.[26-28, 42] DMF is well-known as a carbonylating agent in the synthesis of certain organometallic carbonyl compounds, but it is generally used in a large excess (solvent) as a source of CO in carbonylation reactions.[43, 44]

With the aim to *catalytically* produce primary amines from N-alkylformamides, its potential decarbonylation using transition metal catalysts, based on rhodium, iridium, palladium or ruthenium was briefly investigated (Table 4.4). The results obtained with N-hexylformamide as substrate under mild conditions (eg. at room temperature) show that indeed decarbonylation rapidly proceeds until conversions corresponding to the stoichiometric amount of several transition metal complexes used in the experiments (Entries 1-3,8). With a stoichiometric amount of an Rh/dppp complex decarbonylation proceeded quantitatively (>98% conversion and >90% yield to n-hexylamine) (Table 4.4, Entry 8). Increasing the reaction time (up to 24 hours) and temperature (up to 200 °C), did not improve the decarbonylation conversion or n-hexylamine yield beyond the stoichiometric amount on transition metal complex (see appendix III).

Apparently, for *catalytic* decarbonylation to occur of N-hexylformamide using transition metal catalysts, the removal of CO from the metal center after a decarbonylation event to regenerate the starting complex poses a serious problem. The transition metal complex apparently does not act as a catalyst anymore *after* coordination of a molecule of CO to the metal center. Thus, a catalytic decarbonylation cycle (eqs. i-iv) is effectively frustrated:

$$C_6H_{13}NHCHO + [L_nM^{I}Cl] \rightarrow [L_nM^{III}Cl(H)(C_6H_{13}NHCO)]^{+} \qquad (i)$$

$$[L_nM^{III}Cl(H)(C_6H_{13}NHCO)]^{+} \rightarrow [L_nM^{III}Cl(H)(CO)(C_6H_{13}NH)]^{+} \qquad (ii)$$

$$[L_nM^{III}Cl(H)(CO)(C_6H_{13}NH)]^{+} \rightarrow C_6H_{13}NH_2 + [L_nM^{I}Cl(CO)] \qquad (iii)$$

$$[L_nM^ICl(CO)] \nrightarrow [L_nM^ICl] + CO \tag{iv}$$

The same phenomenon has been reported[37] with the Wilkinson's complex, $[RhCl(PPh_3)_3]$, in aldehyde decarbonylation ($RhCl(PPh_3)_3 + RCHO \rightarrow RhCl(CO)(PPh_3)_2 + RH + PPh_3$). The intermediate Rh-CO species generated in the reaction, are sometimes stable up to 200 °C, and thus are incapable of catalytic decarbonylation below this temperature. Application of a higher reaction temperature is however not a generally feasible option as it often leads to complex degradation and the formation of side-products.[38] Due to the mild reaction conditions and high yield, stoichiometric amounts of Wilkinson's catalyst are still being applied in the synthesis of a variety of target molecules in organic synthesis.[39-41]

Table 4.4. The decarbonylation of N-hexylformamide catalyzed by various catalysts in different conditions[a]

	Metal (Base) 10 mol%	Ligand 20 mol%	conversion % N-hexylformamide	Yield %[b] n-hexylamine
1	$[Rh(cod)Cl]_2$	dppp	10	10
2	$[Ir(cod)Cl]_2$	PPh_3	10	10
3	$RuCl_3.H_2O$	PPh_3	10	10
4	NaOMe		10	10
5	NaOtBu		10	10
6	Na_2CO_3		<1	-
7	$NaOR^F$		<1	-
8[c]	$[Rh(cod)Cl]_2$	dppp	99	92
9[c]	NaOMe		97	89

[a] Reaction conditions: 10 mol% metal (M) or base (B), 20 mol% ligands (L)(M(B):L:formamide=0.5:1:5) T= room temperature; t = 30 min; Solvent: 5 mL diglyme; [b] the yield was determined using decane as external standard; [c] one equivalent catalyst used in the reaction; for more information see appendix III

Decarbonylation of formamide derivatives such as N-formylsaccharin has also been reported using stoichiometric amounts of base.[45] We have briefly explored the possibility of a catalytic decarbonylation of N-hexylformamide catalyzed by strong base (Table 4.4, entries 4-7, 9). It is shown that a rapid decarbonylation indeed did occur under mild conditions with addition of strong base (such as NaOMe). However, the maximal conversion attainable appeared again limited by the stoichiometric amount of strong base present (entries 4, 5).

With the very strong base NaOMe or NaOt-Bu applied in stoichiometric amounts relative to the formamide, n-hexylamine could be produced in higher than 90% yield after only 30 minutes at room temperature (Table 4.4, entry 9). Even at elevated temperatures, we were not able to demonstrate a decarbonylation conversion beyond stoichiometric amounts on base (see appendix III).

Decarbonylation of N-hexylformamide by the strong base NaOMe likely proceeds via initial deprotonation of the formyl H, thus stoichiometrically producing MeOH, CO and the sodium salt of N-hexylamine ($NaNHC_6H_{13}$):

$C_6H_{13}NHCHO + NaOMe \rightarrow C_6H_{13}NHNa + MeOH + CO$ (v)

In order to make the process catalytic in NaOMe, its regeneration should take place via:

$C_6H_{13}NHNa + MeOH \nrightarrow C_6H_{13}NH_2 + NaOMe$ (vi)

However, although the formation of n-hexylamine is observed, seemingly the reaction step (vi) does not proceed as shown, as apparently no catalytic decarbonylation cycle in NaOMe can be sustained. It is shown that the use of weaker bases, such as Na_2CO_3 and $NaOR^F$, does not even result in stoichiometric decarbonylation (Table 4.4, entries 6, 7); these bases apparently are too weak to deprotonate N-hexylformamide.

We can thus conclude that both the development of a *catalytic* transition metal complex as well as a strong-base catalyzed decarbonylation process of N-alkylformamides to generate primary amines remains a challenging goal. Stoichiometric decarbonylation on the other hand is possible, both with several transition metal complexes as well as with strong-base. A possible way out of this catalytic problem could involve a two-step protocol consisting of a base-catalyzed reactive transesterification of N-hexylformamide with methanol continuously removing the produce methylformate, thus producing the desired primary amine (Eq vii), followed by amidation of methylformate with NH_3 to regenerate formamide (Eq. viii) as the substrate for reductive amidation.

$C_6H_{13}NHCOH + MeOH \leftrightarrows C_6H_{13}NH_2 + HCOOMe$ (vii)

$HCOOMe + NH_3 \leftrightarrows HCONH_2 + MeOH$ (viii)

4.3. Conclusions

We have attempted to develop a novel synthetic route for the synthesis of primary amines from alkenes employing hydroformylation, reductive amidation and decarbonylation reactions. In order to obtain N-alkylformamide, the reductive amidation was successfully developed using a highly selective catalytic system comprising rhodium/xantphos/HOTs giving a high N-alkylformamide yield under mild conditions. The use of a larger amount of acid co-catalyst appears to be important for both the nucleophilic addition of the formamide to the aldehyde as well as the substrate specificity in the hydrogenation step. Subsequently, brief investigations of the hydroamidomethylation of alkene with formamide have revealed poor conversion to N-alkylformamide. Previously discovered acidic alcoholic promoters, such as 1,1,1,3,3,3-hexafluoroisopropyl alcohol, for hydroamidomethylation catalysts with higher-alkyl amides, are significantly less effective with formamide as the substrate. This is attributed to excessive formation of acetal by-product from the intermediate aldehyde and alcohol promoter and more in particular to the associated water production under the required more acidic conditions. The produced N-alkylformamides can serve as a source of primary amines by a stoichiometric decarbonylation process with several transition metal complexes as well as strong base. The *catalytic* decarbonylation of N-alkylformamides thus far remains elusive.

4.4. Experimental

4.4.1. Chemicals

The solvent bis(2-methoxyethyl)ether (diglyme) was distilled from CaH_2, deoxygenated and used immediately after the purification process. All other solvents were purged with argon and purified under pressure of dry argon using an Innovative Technologies purification system. The solvents passed through activated columns under low pressure to remove trace impurities. Stainless Steel Schlenk Vacuum line and Sigma Aldrich Air-free flasks allow them to be safely transferred.

1-pentene, butanal, hexanal, heptanal, octanal, nonanal, 2-methylpentanal, benzaldehyde, 3-phenylpropanal, decane (internal standard), para-toluenesulfonic acid (HOTs), bis(2-methoxyethyl) ether (diglyme), 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HOR^F) methanol, ethanol and other solvents, acids and bases were purchased from Acros Organics and Sigma Aldrich, the Netherlands and used as received. The transition metal precursors (acetylacetonato)dicarbonylrhodium(I), chlorido(1,5-cyclooctadiene)rhodium(I) dimer, rhodium(III)chloride, ruthenium(III)chloride, chlorido(1,5-cyclooctadiene)irridium(I) dimer, palladium(II)acetate, bis(dibenzylideneacetone)palladium(0), rhodium on carbon, palladium on carbon and triruthenium dodecacarbonyl were purchased from Acros Organics and Sigma Aldrich, the Netherlands and used as received. The phosphane ligands triphenylphosphane (PPh_3), tri-n-butylphosphane ($P(nBu)_3$), $P(tBu)_3$, PCy_3, $P(nOct)_3$, n-butyldi-1-adamantylphosphane ($P(nBu)(1\text{-}ad)_2$), tris(2,4-di-t-butylphenyl)phosphite ($P(O\text{-}di\text{-}tBuPh)_3$), $P(oMeO\text{-}Ph)_3$, $P(pMeO\text{-}Ph)_3$, $P(2,4\text{-}diMeO\text{-}Ph)_3$, $P(2,6\text{-}diMeO\text{-}Ph)_3$, $P(oEtO\text{-}Ph)_3$, $P(mCl\text{-}Ph)_3$, $P(pCl\text{-}Ph)_3$, $P(m\text{-}Tolyl)_3$, $P(o\text{-}Tolyl)_3$ $P(p\text{-}Tolyl)_3$, 1,3-bis(diphenylphosphanyl)propane (dppp), 1,4-bis(diphenylphosphanyl)propane (dppb), 1,2-bis(diphenylphosphanyl)propane (dppe), oMeO-dppp, pMeO-dppp, oMeO-dppb, pMeO-dppb, oMeO-dppe, tris(2,4-ditert-butylphenyl)phosphite ($P(O\text{-}di\text{-}tBu\text{-}Ph)_3$), 9,9-dimethyl-4,5-bis(diphenyl-phosphanyl)xanthene (xantphos), xantamidite and xantphite were purchased from Strem Chemicals, Germany and Sigma Aldrich, the Netherlands and used as received. The bidentate phsphane ligands bezoxantphos, homoxantphos, DBFphos and POP-xantphos were purchased from Innovative Catalyst Technologies (InCatT B.V.), The Netherlands and used as received. The other phosphane ligands such as 2,7-di-tert-butyl-9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene (tBu-xantphos), 4,6-bis(diphenylphosphanyl)-10,10-dimethyl-10H-dibenzo[b,e][1,4]oxasilane (Si-xantphos), 9,9-dimethyl-4,5-bis(di-orthomethoxyphenyl-phosphanyl)xanthene (oMeO-xantphos), 9,9-dimethyl-4,5-bis(di-paramethoxyphenyl-phosphanyl)xanthene (pMeO-xantphos) and 4,5-bis(di(tert-butyl)phosphanyl)-9,9-dimethylxanthene ($xantphos(tBu)_2$) were generously provided by Shell Global Solutions Amsterdam b.v., The Netherlands and used as received.

4.4.2. Instruments

The stainless steel autoclave reactors (100 ml) were of HEL Limited, UK, equipped with magnetic stirrer, pressure transducer and temperature controlling thermocouple. A Hewlett Packard HP6890 Series auto-sampler GC system was used for regular GC analysis. GC-MS analysis were carried out on an Agilent technologies 7820A GC system series coupled with an Agilent technologies 5975 series GC-MSD system. A glovebox of M. Braun Inert gas-System GmbH, Germany, was used for storing and handling of air-sensitive phosphane ligands. Nuclear magnetic resonance spectra were recorded on a Bruker DPX300 (300MHz) or a Bruker DMX400 (400MHz) spectrometer. A Syringe Pump NE1000 series auto-injector from ProSense B. V. (laboratory and process Equipment Company) was used for the reactive distillation pumping methanol continuously into the reaction mixture. Innovative Technologies PureSolv MD 5 Solvent Purification System was used for drying solvents. All reaction preparations and manipulations were performed using standard Schlenk techniques under an argon atmosphere. The catalytic reactions were carried out under varying syngas pressures and reaction temperatures.

4.4.3. Catalytic high pressure reaction

4.4.3.1. Catalytic reductive amidation of aldehyde with formamide

For all the catalytic experiments the catalyst precursor was formed in-situ in the autoclave by transferring the metal precursor and the selected phosphane ligands into the reactor. In the preparation of a typical catalytic reaction mixture containing solid ingredients that are not air sensitive, 0.005 mmol of $[Rh(cod)Cl]_2$ (2.46 mg, 0.01 mmol of Rh) and 0.0125 mmol of bidentate phosphane ligand or 0.025 mmol or monodentate phosphane ligand were weighed in air and transferred into an autoclave. The autoclave was closed and subsequently filled with argon using a Schlenk line connected to one of the valves of the autoclave. Through another valve under a continuous flow of argon subsequently were added: 25 ml of dried and degassed diglyme as solvent, 3.125 mmol (0.605 ml) decane as an internal standard, 5 mmol (0.615 ml) hexanal and 6 mmol (0.199 mL) formamide followed by 0.05-0.2 mmol HOTs. Then the reactor was inserted into the heating block and connected to the gas line of the reactor block with a continuous flow of N_2 gas through the gas line of autoclave to remove the air inside the gas line. The autoclave reactor was flushed three times with N_2 and one time with H_2 and finally pressurized with hydrogen gas. The reaction mixture was stirred at 500 rpm for 30 min to ensure complex formation.

In the set of experiments using air-sensitive ligands such as $P(nBu)_3$, $P(nBu)(1\text{-ad})_2$, bcope and di-tBu-xantphos, in a glovebox the metal precursor complex and ligand (for some experiments with other additives like acid), were weighed into a Schlenk flask and dissolved in 10 ml of dried and degassed diglyme; dissolution generally was complete in about 2-3 minutes as was visible by the formation of a transparent yellowish solution. The flask was then connected to a Schlenk line and the solution was transferred through the valve of a reactor under a continuous flow of argon into the 100 ml stainless steel autoclave reactor. The procedure for gas intake in the autoclave was carried out as described above.

The reaction mixtures were heated up to 40 °C, 60 °C, 80 °C or 100 °C (within 30 min) under stirring at 500 rpm. All reaction conditions of the catalytic process were controlled by computerized software panels. After standing for four or eight hours at this temperature, the autoclave was cooled down to room temperature over about one hour. The autoclave was then slowly vented to atmospheric pressure.

After each catalytic run the reaction mixture was taken from the reactor and immediately analyzed with gas chromatography. Calibration lines for each analyte were used to determine the conversion of the substrates and yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples.

4.4.3.2. Catalytic hydroamidomethylation of 1-pentene with formamide

For all the catalytic experiments the active catalyst precursor was formed by *in-situ* in the autoclave by transferring the metal precursor and the selected phosphane ligands. In the preparation of a typical catalytic reaction mixture 0.01 mmol of $[Rh(acac)(CO)_2]$ (2.58 mg) and 0.02 mmol of bidentate phosphane ligand or 0.04 mmol of monodentate phosphane ligand were weighed and transferred into an autoclave. The autoclave was tightly closed and subsequently filled with argon with use of a Schlenk line that was connected to one of the valves of the autoclave. Through another valve under a continuous flow of argon subsequently was added 10 mL of dried and degassed diglyme or 8 ml of dried and degassed diglyme, 2 ml of HOR^F, 3.125 mmol (0.605 ml) decane as an internal standard, 5 mmol (0.548 ml) 1-pentene and 5 mmol (0.166 ml) formamide followed by 0.05-0.2 mmol HOTs. Then the reactor was inserted into the heating block and pressurized with 50 bar ($CO/H_2=1/2$) syngas. This reaction mixture was stirred at 500 rpm for 30 min to ensure that complex formation was complete. The reaction mixture was heated up to 60-100 °C (within 30 min) under stirring at 500 rpm. All reaction conditions of the catalytic process were controlled by computerized software panels. After standing for eight hours at this temperature, the autoclave was cooled down to room temperature over about one hour. The autoclave was then carefully vented to atmospheric pressure.

After each catalytic run the reaction mixture was taken from the reactor and at once analyzed by gas chromatography. Calibration lines for each analyte were used in determining the conversion of the substrates and yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples.

4.4.4. Decarbonylation of N-hexylformamide

A 50 ml two neck round-bottom flask, fitted with a condenser and connected to the schlenck line, (or 100 ml autoclave) was charged with 0.72 ml N-hexylformamide (5-10 mmol) and 0.5-1 mmol of a catalyst under argon. Then 5 ml of dried and degassed solvent (diglyme or other solvents) was injected into the flask under a continuous flow of argon. The flask was fitted with a reflux condenser. The mixture was stirred or stirred and heated to the desired temperature for 30 minutes or longer. After each catalytic run the reaction, the external standard decane was added and then the mixture was taken from the flask and at once analyzed by gas chromatography. Calibration lines for each analyte were used in determining the conversion of the substrates and yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples.

4.4.5. Synthetic procedures

4.4.5.1. Synthesis of N-hexylformamide

Following the reported procedure, A 500 ml round-bottom flask was charged with 33 ml hexylamine (0.25 mol), 11.5 ml formic acid (0.30 mol, 1.2 eq.) and 250 ml toluene. The flask was then attached to a Dean-Stark apparatus and heated up to reflux under stirring. The flask was insulated with aluminium foil. After 18-24 h the reaction was stopped and the flask was cooled down to room temperature. Then volatiles and solvent were removed by evaporation under reduced pressure. The product was isolated as a transparent viscous liquid with a near to quantitative yield.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K); $\delta_H = 8.15$ (s, 1H, CHO), 6.29 (s, 1H, NH), 3.27 (q, 2H, CH_2), 1.52 (m, 2H, CH_2), 1.31 (s, 6H, 3* CH_2), 0.90 (m, 3H, CH_3).

4.4.6. GC and GC-MS analysis

GC spectra of typical **reductive amidation and hydroamidomethylation with formamide** are shown in the appendix IV with the assignment of products. 1 µL Crude reaction mixture containing internal standard was injected into a Hewlett Packard HP6890 Series auto-sampler GC system with column HP-1MS UI (30m*0.250mm*1.00µm). All the solvents have been assigned by comparing to their standard GC spectra. All the retention values of substrate and product to decane have been determined using commercially available or isolated standard chemicals.

Analysis conditions: 130 ºC (5 min), ramp 50ºC/min to 300 ºC, 300 ºC (3.6 min) (12 min in total).

GC-MS Method: 1 µL Crude reaction mixture containing internal standard was injected into a GC HP7820 Series auto-sampler GC system with column DB-5MS UI (30m*0.250mm*1.00µm) equipped with MSD 5975 Agilent series. All the solvents have been ignored by comparing to their standard GC spectra. All the retention values of substrate and product to decane have been determined using commercially available or isolated standard chemicals.

Analysis conditions: 100 °C (2.5 min), 20 °C / min to 250 °C, 250 °C (5 min) (15 min in total).

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